1042-95 Significant Enhancement of Therapeutic Ultrasound-Induced Thrombolysis Using Perfluorocarbon-Exposed Sonicated Dextrose Albumin Microbubbles

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In the presence of high intensity ultrasound, microbubbles(MB) cavitate (expand and collapse) and release energy which has been shown to catalyze various physical and chemical processes such as thrombolysis (TL). Since sonicated perfluorocarbon-exposed dextrose albumin (PESDA) is a stable form of MB, we hypothesized that they would be capable of enhancing therapeutic ultrasound (TUS)-induced TL. Accordingly, we measured % clot lysis (%CL) of equally-sized thrombi (0.99 ± 0.12 milligrams) made from freshly drawn blood incubated for two hours and then exposed in vitro to TUS (1.5 Watts/cm²). The thrombi were bathed in four milliliters (ml) of either saline (S), urokinase (UK) (20,000 Units), PESDA (4 ml), or UK and PESDA combined (10,000 Units UK + 2 ml PESDA). A total of 96 separate samples were compared. Results are shown:

	US + S	US + UK	US + PESDA	US + UK + PESDA
% CL	25 ± 16	49 ± 8*	44 ± 20*	69 ± 9**

*p < 0.05 compared to US + S, S, UK, and MB; **p < 0.05 compared to all.

In the absence of TUS, PESDA produced no TL (3 ± 3%CL), and UK alone produced only 18 ± 2%CL. The significantly better TL seen with PESDA + UK + US occurred despite using only half the doses of UK and PESDA that were used when each agent was tested alone. We conclude that (a) PESDA alone can significantly enhance TUS-induced TL and (b) there appears to be an additive thrombolytic effect by adding both UK and PESDA to TUS-induced clot lysis.

1042-96 Oral Anticoagulation Control: Centralized Clinic vs. Individual Physicians

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The number of patients maintained on chronic oral anticoagulation with warfarin has rapidly increased over the past several years. Complications related to warfarin use as well as thrombotic and embolic complications are directly related to maintaining the patient in the therapeutic range as measured by INR. Centralized management of warfarin therapy was evaluated to determine if therapeutic control of INR was superior to individual physician management.

The study group was comprised of 100 patients consecutively chosen from 925 patients managed in a large anticoagulant clinic (AC). To be included in the study group, each patient had to be monitored for at least three months by their individual physician and three months by the AC. Patients were classified by reason for anticoagulation and by type of physician managing their anticoagulation. The reason for anticoagulation was atrial fibrillation (40 pts), valvular heart disease (n = 16), cardiomyopathy (n = 8), PVD (n = 3), pulmonary embolism (n = 4), coronary artery disease (n = 3), deep venous thrombosis (n = 8), CVA (n = 9), TIA (n = 4), misc. group (n = 5). Internists followed 44 patients, cardiologists 50 patients and surgeons 6 patients. Individual physician-managed patients were found to be out of the therapeutic INR range 47% of the time compared with 24% of the patients managed by the anticoagulant clinic ($p < 0.001$). No significant difference was found by physician specialty in management.

We conclude that the anticoagulant clinic provides better control of warfarin therapy than individual physician management. Given that better control produces fewer complications, this form of anticoagulation management appears preferred.

1042-97 PFO Closure to Prevent Recurrent Stroke or TIA in Young Adults

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Whether surgical closure of patent foramen ovale (PFO) in young adults after cerebral ischemic events prevents recurrence remains questionable. Eighty-five pt less than age 50 (mean 39 ± 8 yr) were retrospectively identified with stroke (n = 58) or TIA (N = 27) and subsequent unequivocal demonstration of a PFO by transesophageal echo. Comorbid conditions were atrial fibrillation (AF) in 2%, diabetes in 2%, hypertension in 16%, and deep venous thrombosis in 5%. Treatment was aspirin (ASA) or warfarin (n = 59), initial ASA or warfarin followed by PFO closure (n = 14), initial PFO closure (n = 10), and no therapy (n = 2). Operative morbidity and mortality of PFO closure were 0%. Recurrent events occurred in 11 pt without and 1 pt with PFO closure (mean follow-up 2.9 ± 1.9 yrs). Univariate proportional hazard (PH) analyses suggested the following factors to be associated with recurrence risk: stroke as index event [hazard ratio (HR) 0.42, 70% confidence interval (CI) (0.23, 0.75) p = 0.14]; smoking [HR 2.9 (1.49, 5.67) p = 0.11]; AF [HR 3.8 (1.34, 10.85) p = 0.20]. No PFO closure seemed to be associated with higher recurrence risk [HR 3.2 (1.1, 9.1)], but these results could be attributable to chance (p = 0.19). There was no difference in recurrence risk with use of either ASA or warfarin. We conclude, (1) the overall cumulative probability of having a recurrent embolic event with PFO is 0.20 at 5 years (CI:0.08, 0.30), (2) PFO closure may be associated with a greater than 50% reduction in recurrence risk, and (3) surgical closure of PFO can be accomplished at minimal risk in young adults.

1042-98 Effects of Introducing Ultra-Low Dose Warfarin and Aspirin on Fibrin D-Dimer and Beta-Thromboglobulin as Markers of Intravascular Thrombogenesis and Platelet Activation in Chronic Atrial Fibrillation

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Chronic atrial fibrillation (AF) is an arrhythmia which is associated with a high risk of stroke. To determine the effects of warfarin and aspirin on thrombogenesis and platelet activation in AF, we measured sequential changes in plasma fibrin D-dimer (an index of fibrin turnover and intravascular thrombogenesis, AGEN-ELISA) and beta-thromboglobulin (β-TG, a measure of platelet activation, AMERSHAM) in 51 patients (34 male, 17 female; mean age 70.4 years ± s.d. 7.4) with chronic AF before and at 2 and 6 weeks following randomisation to either 1 mg warfarin or 300 mg aspirin (Phase 1). All patients were then started on standard warfarin therapy, aiming for a target INR of 1.5–2.5 (Phase 2) with samples at 2 and 6 weeks afterwards. Pretreatment results were compared to 26 healthy controls in sinus rhythm (16 male, 10 female; mean age 72.7 years ± 9.9). Baseline (pretreatment) β-TG and D-dimer levels in patients with AF were significantly elevated compared to controls (β-TG: 181 vs 91 ng/ml, median difference 79 ng/ml, paired Wilcoxon test, $p < 0.001$; D-dimer: 220 vs 100 ng/ml, median difference 106 ng/ml, $p = 0.0001$). In phase 1, there were no significant changes in levels of D-dimer or β-TG, despite warfarin 1 mg or aspirin 300 mg. However, with standard warfarin therapy (Phase 2), there was a reduction in median β-TG at 6 weeks (207 vs 172 ng/ml; $p = 0.025$) and a sequential reduction in median D-dimer levels, at 2 weeks (220 vs 139 ng/ml; $p = 0.001$) and at 6 weeks (220 vs 110 ng/ml; $p < 0.001$) when compared to baseline levels. *Conclusion* — Patients with AF have increased intravascular thrombogenesis and platelet activation, as indicated by the high D-dimer and β-TG, when compared to patients in sinus rhythm. Introduction of ultra-low dose (1 mg) warfarin or aspirin 300 mg does not significantly alter these markers, although conventional warfarin therapy (target INR 1.5–2.5) reduces β-TG and D-dimer levels. This is consistent with the beneficial effect of warfarin in preventing stroke in patients with atrial fibrillation.

1043 Pharmacologic Inhibition of Myocyte Growth

Wednesday, March 27, 1996, 3:00 p.m.–5:00 p.m.
Orange County Convention Center, Hall E
Presentation Hour: 3:00 p.m.–4:00 p.m.

1043-99 ACE Inhibitors Induce Apoptosis in the Vascular Wall: Evidence From Rat Carotid Artery and Human Atherectomy Samples

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Recent animal data have shown that ACE inhibitors (after a sufficient pretreatment period) suppress neointima formation in injured rat carotid arteries. We hypothized that ACE inhibitors (AI) can induce apoptosis and thereby modulate the responsiveness of vascular smooth muscle cells (SMCs) to mitogenic and migratory stimuli. 7/14 Sprague Dawley rats (350 g) were treated with the AI benazepril (10 mg/kg p.o.; Cibacen; Ciba Geigy) for 14 days and then sacrified. Morphometric analysis of serial carotid sections showed a mean cell density of 3817 ± 232 cells/mm² (x ± SD) for AI rats, and 4208 ± 697 cells/mm² for placebo animals (p = 0.13). TUNEL testing revealed a high proportion (31 ± 13%) of immunoreactive (apoptotic) cells in AI rats, whereas markedly ($p < 0.01$) lower signalling (6 ± 4%) was observed in control rats. In order to substantiate the functional significance of this finding, we used a cell culture model to stimulate SMC outgrowth: (i.e. migration and proliferation). Notably, AI tissue explants exhibited SMC outgrowth after 4.2 ± 0.4 days